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Two kinds of rule regulating human subjects research

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ABSTRACT

Alan Wertheimer argues that before we promulgate some rule regarding the conduct of research on human subjects we ethically ought to consider the consequences of the rule being followed. This ethical requirement has an exception, though, Wertheimer maintains: it doesn't apply to rules that are not motivated by considerations of outcome. I agree that there is an exception to be made to Wertheimer's proposed ethical requirement, but not Wertheimer's exception. The important distinction is not that between rules motivated by considerations of outcome and rules motivated otherwise, but between rules designed to enforce ethics and rules not so designed. Before we promulgate the latter kind of rule, we are ethically required to consider the consequences of doing so. This is not so for the former kind of rule. My exception, unlike Wertheimer's, yields the conclusion that we should promulgate, regardless of the consequences of doing so, a rule requiring that the potential benefit to the subject of participation in a study outweigh the risks. This rule *is* motivated by considerations of outcome, so it would land on the wrong side of Wertheimer's divide. But it's also designed to enforce ethics, so it lands on the correct side of my divide.

KEYWORDS: Research ethics, regulation, promulgations, standard of care, incentives

Moral philosophy suffered a great loss when Alan Wertheimer passed away earlier this year, as the legions of people familiar with his excellent work on coercion, exploitation, and consent will attest. Perhaps less well-known is that at the end of his career, when he turned his attention to human subjects research, Alan devoted his time to saying some unpopular things that absolutely needed to be said. (He was certainly doing so in the article to which I'm responding here.) On a personal note, Alan was a kind,

generous mentor to me, and I learned a great deal from our discussions. He was always up for a lively give and take; so in that spirit, on we go.

Various organizations, such as the World Medical Organization and CIOMS, have taken it upon themselves to publish rules for the conduct of medical research on human subjects. Although these rules don't have the force of law—at least not directly—they're quite influential. And so, Alan Wertheimer argues in a recent article that the bodies issuing these rules, or making these 'promulgations' as we might say, should consider the consequences of their doing so when doing so.[1]

I argue here that Wertheimer makes one serious false move in defending his conclusion. Ultimately I want to show how the flaw can be fixed, and in a way that Wertheimer has no strong reason to resist. First, however, I briefly recapitulate Wertheimer's argument. Then I then take a closer look at a crucial part of that argument, in which Wertheimer tries, unsuccessfully in my view, to block a likely objection.

Wertheimer's conclusion, that the consequences of rule-promulgation in the area of human subjects research should be taken into account, is a generalization from four cases, each of them an already-promulgated rule. For each case, Wertheimer provides a plausible story as to how promulgating such a rule could yield bad consequences for the research subjects themselves or the broader community—the very entities the promulgation of the rules is supposed to benefit.[2] I'll summarize here each of the four examples:

The Responsiveness Principle: Studies conducted in low- and middle-income countries (LMICs) 'should be responsive to the health needs of the host country'.[3]

Wertheimer points out that promulgating this rule could lead to some studies that would otherwise have been conducted in developing countries being either not conducted or moved to a developed country. He invites the reader to imagine that a pharmaceutical company wants to conduct a study, in Uganda, of a new hypertension drug against an existing drug. If hypertension isn't a health priority in Uganda, as it seems not to be, then The Responsiveness Principle rules out conducting this study. But the study not being conducted in Uganda would be bad for the potential Ugandan subjects, since they actually do suffer hypertension.

Standard of Care: A new intervention may not be tested 'against a placebo when proven effective treatment is available unless, perhaps, a placebo-controlled trial is necessary to generate the relevant scientific information and there is little risk to the subject in not receiving the intervention'.[4]

Wertheimer notes that in response to the Standard of Care rule, study sponsors have, in the past, changed their plan regarding where to site a planned study. This can have, and has had, serious negative consequences for the people who would have had the opportunity to serve as research subjects if the plan had not been changed.

Post-Trial Treatment: A study may not be conducted 'if there is good reason to believe that a product developed or knowledge generated by [the study] is unlikely to be

1 Alan Wertheimer, *The Ethics of Promulgating Principles of Research Ethics: The Problem of Diversion Effects*, 2 J. L. & Biosci. 2 (2015).

2 *Id.* at 28.

3 *Id.* at 3.

4 *Id.* at 16.

reasonably available to, or applied to the benefit of, the population of a host country or community after the conclusion of the research'.[5]

Wertheimer points out that there will often be a cost associated with abiding by the Post-Trial Treatment rule. This extra cost could render unaffordable some studies that would otherwise be affordable, thereby depriving the world of the benefit of the knowledge it would have generated and depriving the would-be study subjects of any benefits they would have gained by participating. Moreover, it could cause some studies to be conducted in developed countries that would otherwise have been conducted in developing countries, since in developed countries the national health service might pick up the cost of providing the population access to the newly proven health intervention. This is unfortunate, since there is more good to be done in developing countries.

Ancillary Care: A study may not be conducted unless ancillary care is provided to the study subjects.

Ancillary care is treatment "'beyond what is necessary to implement a study's design safely and validly" and is also beyond any (contractual) treatments that investigators may offer in order to recruit and enroll a sufficient number of participants'.[6] Wertheimer points out that providing ancillary care comes at a cost and therefore could lead to an otherwise affordable study becoming unaffordable, thereby depriving the world of the knowledge that would otherwise have been gained. And, again, it could also lead to a study being sited in a place where potential subjects already have good health care, since this would entail there being less ancillary care to provide.

Because his worries about the four rules listed above each stem from a concern that the good consequences of potential studies not be lost out on, Wertheimer anticipates that he might be criticized as simply assuming a consequentialist framework for assessing the validity of rules regarding human subjects research.[7] In response, he points out that one cannot validly infer consequentialism from the principles to which he appealed in raising worries about the four rules. Wertheimer furthermore goes on endorse the idea that there are two rules that researchers should follow even when the consequences of doing so are bad overall, rules I will label 'Informed Consent' and 'Overall Benefit'.

Informed Consent: A person may not be enrolled as a subject without his/her informed consent.

Overall Benefit: A person may not be enrolled as a subject unless the potential benefits to him/her outweigh the potential harms to him/her.

This is a fair response, but of course the fact remains that Wertheimer's criticisms of the promulgation of the four rules (as I will henceforth collectively refer to The Responsiveness Principle, Standard of Care, Post-Trial Treatment, and Ancillary Care) are consequence-based. This invites the question of what makes the promulgation of some rules, including (apparently) the four rules, liable to consequence-based criticism, and the promulgation of other rules, including (apparently) Informed Consent and Overall Benefit, immune.

Wertheimer is aware of this worry as well. He points out that each of the four rules is motivated by a concern for a certain sort of consequence: the well-being of individuals. So criticizing the promulgation of those rules for possibly causing individuals to

[5] *Id.* at 18.
[6] *Id.* at 21, quoting Richardson and Belsky.
[7] *Id.* at 28.

enjoy less well-being constitutes criticizing them on grounds of possibly violating *the very principle that motivates them*. Another way to put this is that Wertheimer's criticism of the promulgation of each of the four rules is an internal criticism.

So far, so good. However, the natural question to ask next is whether the promulgation of Informed Consent or Overall Benefit might be liable, on the same grounds, to consequence-based criticism. Seemingly anticipating this move as well, Wertheimer points out that Informed Consent has a deontological form. This may be his way of saying that criticizing the promulgation of Informed Consent on grounds of possibly leading to bad consequences would not qualify as lodging an internal criticism. What Wertheimer doesn't address is whether the promulgation of Overall Benefit is liable to consequence-based criticism. He clearly believes that it isn't, yet the fact remains that it does seem liable to one. The most obvious defense of promulgating Overall Benefit is that doing so works to the benefit of actual and potential study subjects. This is a consequence-based defense, and so criticizing the promulgation of Overall Benefit for possibly leading to bad consequences would constitute lodging an internal criticism. Moreover, such a criticism would be rather compelling: What if, as seems likely, holding human subjects research to an Overall Benefit rule causes some studies that would otherwise have been conducted to not be conducted? This being the case, the world is thereby deprived of the knowledge that those studies would have generated. This is a bad consequence.

This leaves Wertheimer in a pickle. It appears he must either (a) insist that sometimes it isn't legitimate to criticize consequence-based rule-promulgations on grounds of possibly leading to bad consequences, (b) argue that the promulgation of Overall Benefit is not consequence-based, or (c) admit that whether we should promulgate Overall Benefit depends on the likely consequences of doing so, as is the case (according to Wertheimer) with the four rules.

I assume that Wertheimer wouldn't be willing to take any of these three options. Fortunately, the trilemma is only apparent. If Wertheimer were willing to change slightly his criticism of the promulgation of the four rules, then he could stand by those criticisms and also his endorsement of Overall Benefit. I turn now to showing how that can be done.

I begin by calling attention to how Wertheimer initially motivates his claim that we should attend to the consequences of promulgating a rule before promulgating it. He does so by bringing forward four examples of rules outside the domain of human subjects research—rules for which it is uncontroversial, or at least less controversial, that we should attend to consequences when deciding whether to promulgate them. They are as follows.

i. Establishing a speed limit on a highway.[8]
ii. Requiring that small children traveling on planes be put in a child safety seat.[9]
iii. Changing the tax on cigarettes.[10]
iv. Changing the rate of income tax to which high earners are subject.[11]

[8] *Id.* at 2.
[9] *Id.* at 3.
[10] *Id.* at 4.
[11] *Id.* at 5.

I submit that one feature each of these rules has in common is that its purpose is *not* the enforcement of ethics. There is no ethical fact of the matter as to what speed people should drive on the highway—or at least no uniform fact that a speed limit law could enact. And it's probably not unethical—that would be awfully harsh—for a parent not to put his/her small child in a safety seat when traveling by plane. Similarly, there is no ethical fact of the matter as to what the tax on cigarettes should be. That is, unless we can make an argument that tax revenue on cigarettes are what smokers morally owe to the rest of the population for driving up health care costs; Wertheimer, however, cites as motivations for a cigarette tax reducing the number of people who smoke and raising revenue. By contrast, there may be an ethical fact of the matter as to what rate of income tax high earners should pay, but enforcing that obligation is probably not the *purpose* of the income tax—i.e. it isn't why we have one. And Wertheimer makes no reference to that motive in his discussion of the income tax; he simply alludes to the state's need for revenue.

With that premise laid out, I want to suggest a first move for Wertheimer to make by way of extricating himself from the trilemma in which we left him.

First Move: Claim that the purpose of The Four Rules is, likewise, not the enforcement of ethics.

Admittedly, Wertheimer clearly doesn't want to say this.[12] But if he *did* say this, he could then, without any inconsistency (as I will argue below), make this second move.

Second Move: Claim that promulgating Overall Benefit *does* have the purpose of enforcing ethics.

Having made these two moves, Wertheimer could proceed to this Third Move.

Third Move: Maintain that when it comes to promulgating rules that are not designed to enforce ethics, we are ethically required to take into account the consequences of doing so.

I've argued for this claim elsewhere,[13] in the service of defending the same conclusion at which Wertheimer arrives: with respect to *some* rules regarding the conduct of human subjects research (not, for instance, Informed Consent and Overall Benefit), organizations should take into account the consequences of promulgating those rules before doing so. Wertheimer himself would have no problem with making this move, and when combined with the first move it gets Wertheimer to the conclusion he wants to reach with respect to the four rules. Where Wertheimer and I depart, however, is that I believe (and will argue below) that Wertheimer should make this fourth move.

Fourth Move: Insist that when it comes to promulgating rules that *are* designed to enforce ethics, we are not ethically required to take account of the consequences of doing so.

This, combined with the second move would get Wertheimer to the conclusion he wants to reach regarding Overall Benefit, namely that ethics does not require that we take account of the consequences of promulgating it.

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[12] He portrays organizations like the WMA and CIOMS as being in the business of promulgating *ethical* rules for the conduct of human subjects research, and he concludes his article by saying that such bodies should attend to 'the ethics of promulgating *the ethics of* conducting research' (*Id.* at 32, emphasis mine).

[13] Benjamin Sachs, *The Case for Evidence-Based Rulemaking in Human Subjects Research*, 10 Am. J. Bioethics 3 (2010).

I don't have the space here to argue thoroughly for my claim that there is no inconsistency in making the First and Second Moves. But let me say two things.

First, Overall Benefit follows directly from the principle of Beneficence, one of the canonical principles of bioethics (the others being Respect for Persons and Justice). By contrast, none of the four rules follows in any straightforward way from a canonical principle. Standard of Care, Post-Trial Access and Ancillary Care each require that a certain *kind* of benefit (or chance of benefit) be bestowed on research subjects. Similarly, Responsiveness requires that a chance of a certain *kind* of benefit be bestowed on the country that hosts the study—namely, the production of useful knowledge regarding a health condition that is a priority in that country. These requirements that are truly bizarre from the perspective of the Principle of Beneficence, which underwrites a concern only for the *amount* of benefit conferred as opposed to the kind.[14]

Second, the basic principles underlying each of the four rules are ones that we obviously reject when applied to other domains of human activity. Take for instance, the domain of employment.[15] Suppose there were a factory in Jamaica producing heavy winter coats. Those who own and run that factory might be guilty of no wrongdoing at all, despite their violating the analogues of each of the four rules. For instance, the factory wouldn't be responsive; Jamaicans have no need for heavy winter coats. And they probably wouldn't reward their workers with some of the winter coats they've produced, thus running afoul of the analogue of Post-Trial Access). By contrast, it's not clear that we would reject Overall Benefit as applied to other domains of life. Admittedly, it's not clear that we accept it either. We consider employment contracts valid even when we think that the worker isn't receiving enough money and benefits to compensate for whatever might be bad about having to do the work. But this might not be because we deny the Overall Benefit rule as applied to employment. Rather, it might simply reflect a sensible reluctance on our part to enforce our judgments about what's good for other people. Some of the facts about what constitutes well-being for an individual are contingent on her tastes, values, the commitments she has made, etc. Therefore, it seems that the enforcement of an Overall Benefit rule in the domain of employment, in order to be carried out accurately, would require drastic intrusion into individuals' personal lives. It might well cause more harm than good. (Talk about a case of bad side-effects of rule-promulgation!) So our refusal to enforce an Overall Benefit rule in the domain of employment says little if anything about our acceptance of the ethical claim behind the rule.

As to the fourth move, I admit that it would be controversial. Peter Singer has argued that what ethical rules we should promulgate *does* depend on the potential consequences of their promulgation. Troublingly, Wertheimer makes note of this with apparent approval.[16] But nothing else Wertheimer says commits him to agreeing with Singer. Granted, it would be inconsistent for a consequentialist to deny what Singer says, but Wertheimer is not a consequentialist (remember, he endorses promulgating Informed Consent, without concerning himself with the question of what

[14] The argument of this paragraph draws on Benjamin Sachs, *Going from Principles to Rules in Research Ethics*, 25 BIOETHICS 9 (2011).

[15] Here, I draw on the argument I made in Benjamin Sachs, *The Exceptional Ethics of the Investigator-Subject Relationship*, 35 J. MED. PHILOS. 64 (2010).

[16] Wertheimer, *supra* note 1, at 24.

consequences that might bring), so no such pressure applies to him. One might try to back Wertheimer into a corner by suggesting that surely the consequences of promulgation matter any time the rule in question is motivated by consideration of consequences, as is the case with Overall Benefit. Notice, however, that Overall Benefit is motivated by consideration of the consequences *for people who serve as research subjects*. So if promulgating Overall Benefit could be shown to have negative consequences specifically for people who serve as research subjects then, yes, even a non-consequentialist would be under considerable pressure, from considerations of consistency, to concede that he shouldn't promulgate it. But it's hard to see how that might be shown.